ACIP Evidence to Recommendations Framework – Japanese Encephalitis Vaccine

Question: Should inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC) be recommended for use in persons aged ≥2 months at risk of travel-related exposure to Japanese encephalitis (JE) virus?
Population: Persons aged ≥2 months traveling to JE risk areas
Intervention: JE-VC administered as a 2-dose primary series
Comparison: No JE vaccination
Outcomes: The benefits considered critical outcomes for which there were data available included short and long-term seroprotection using the established immunologic correlate of protection (JE virus neutralizing antibodies at a PRNT50 titer ≥10). The harms considered critical outcomes were serious adverse events and adverse events of special interest (i.e., fever, rash, hypersensitivity/urticaria, neurologic adverse events, and medically attended adverse events).

Background: JE is a mosquito-borne disease that occurs throughout most of Asia and parts of the western Pacific. JE virus is transmitted in an enzootic cycle between mosquitoes and amplifying vertebrate hosts, primarily pigs and wading birds. JE virus is transmitted to humans by infected mosquitoes. Humans usually do not develop a level or duration of viremia sufficient to infect mosquitoes, and therefore are considered dead-end hosts. JE virus transmission occurs primarily in rural agricultural areas.

JE-VC (manufactured as IXIARO) is the only JE vaccine licensed and available in the United States. JE-VC is manufactured by Valneva Austria GmbH. In March 2009, the US Food and Drug Administration (FDA) licensed JE-VC for use in adults aged ≥17 years. In June 2009, the ACIP approved recommendations for use of JE-VC in adults. In September 2010, FDA approved a JE-VC booster dose for adults and, in February 2011, adult booster dose recommendations were approved. In May 2013, FDA approval for use of JE-VC was extended to include children aged ≥2 months. A GRADE for use of JE-VC in children was presented to ACIP and recommendations for pediatric use of JE-VC were approved in June 2013. In April 2018, FDA approved the pediatric booster dose.

There are no efficacy data for JE-VC. However, a JE virus 50% plaque reduction neutralization test (PRNT50) titer of ≥10 is an established immunologic correlate of protection. JE-VC was licensed based on its ability to induce neutralizing antibodies and a non-inferiority comparison to a licensed inactivated mouse brain-derived JE vaccine (JE-MB [manufactured as JE-VAX]). JE-MB is no longer available in the United States. At the time of licensure, JE-VC had been studied in <5,000 adults.

Since JE-VC's licensure, more than 1 million doses have been distributed in the United States. Since the 2013 GRADE, additional immunogenicity and safety data from clinical trials and surveillance activities have become available. The ACIP JE Vaccine Work Group used GRADE methods to review and evaluate these newly available data. Additional factors also were assessed in considering the JE vaccine recommendations, as outlined in the Evidence to Recommendations (EtR) framework. The results of the work group's deliberations and the JE vaccine recommendations are presented below.

Additional information supporting the ACIP recommendations on the use of JE vaccine can be found here.

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	CRITERIA	JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem of public health importance?	*No* ☐ *Probably no* ☐ *Uncertain* ☐ *Probably yes* ☐ *Yes* ☐ *Varies* ☒	JE is of public health importance in Asia and parts of the Western Pacific. • Leading vaccine-preventable cause of encephalitis in Asia, with an estimated 67,900 cases annually. • In the highest risk areas prior to vaccination programs, incidence rates as high as 20 cases per 100,000 children per year were reported. JE cannot be considered a substantial public health problem for U.S. travelers overall. • A JE vaccine was first licensed for use in the United States in 1992. • In the 25-year period from 1993–2017, 12 JE cases were reported among U.S tourists or expatriates, with a median of 0 reported cases per year (range: 0–2 cases). • Based on the 12 reported cases from 1993–2017 and approximately 4–5 million U.S. citizen trips annually to Asia, the overall estimated risk is <1 case per million trips to Asia. Importation of JE virus by an infected traveler is not a public health concern • There is no risk of subsequent local transmission from an infected traveler. JE is an important individual concern for some travelers, especially those with higher risk itineraries. • Risk for JE varies based on travel duration, season, geographic location, activities, and accommodations. • For some persons, such as those taking up long term residence in rural areas of Asia, risk might	

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			approach a similar level to populations of endemic areas. When disease occurs, only supportive treatment is available and the outcome is often severe. • <1% of infected people develop encephalitis, but among encephalitis cases there is a 20–30% mortality rate, and 30–50% of survivors have significant sequelae. • JE can be a serious problem for individual travelers, and substantial resources might be needed to care for a person with a serious long-term disability. The costs and benefits of immunization are primarily at the individual rather than societal level • JE vaccine is paid for out-of-pocket by most civilian travelers, is typically not covered by insurance, and is not covered under the Vaccines for Children program. **Overall conclusion:** JE is a public health problem in JE endemic countries. For the U.S. population, it is an individual traveler rather than societal concern, so the question of public health importance is not directly applicable. In addition, JE vaccine typically is paid for by the traveler themselves. However, since certain travelers might have sufficiently high risk to warrant vaccination, the consensus was that public health importance "varies" related to the individual person's itinerary and activities.	

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BENEFITS & HARMS	How substantial are the desirable anticipated effects?	*Trivial* ☐ *Small* ☐ *Moderate* ☐ *Large* ☒ *Don't know* ☐ *Varies* ☐	A Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) was completed. Evidence used to evaluate seroprotection at 1 month after vaccination with JE-VC was from 12 studies, including four randomized controlled trials (RCTs). • Of 1,673 JE-VC recipients in the 12 studies combined, 1,582 (95%) were seroprotected at 1 month after the 2-dose primary series. • Seroprotection rates in 11 of the 12 studies were ≥95% (see Additional Information). • In the four RCTs, seroprotection rates in JE-VC recipients were similar to or higher than seroprotection rates for recipients of the comparator vaccines. • When data from the four RCTs were combined and weighted using a random effects model, there was no significant difference in seroprotection rates between recipients of JE-VC and the other JE vaccines. Evidence used to evaluate seroprotection at 5 to 6 months after vaccination with JE-VC was from six studies of JE-VC, including two RCTs. • Of the 941 JE-VC recipients in the six studies combined, 864 (92%) were seroprotected at 5 to 6 months after the 2-dose primary series. • Seroprotection rates in the individual studies ranged from 83% to 100%. • The data from the two RCTs in adults showed that a significantly higher proportion of JE-VC recipients were seroprotected compared with subjects who received mouse brain-derived JE vaccine.	Seroprotection rates were much lower in the only study conducted specifically among elderly subjects, with 128 (65%) of 197 adults aged ≥64 years seroprotected at 42 days after the primary series. These data were considered by the work group and presented to ACIP in October 2015 and were submitted to FDA. While there are lower seroprotection rates in older adults, there are no data on the safety, immunogenicity, or optimal timing of a possible third primary series dose or early booster dose for older adults. The majority of data are in adults; however, data from the three pediatric studies, supported by adult data, were

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			Overall conclusion: The work group concluded the desirable anticipated effects were large.	considered sufficient for pediatric licensure. Herd immunity is not a consideration as JE virus circulates in an enzootic cycle in the environment and is not transmitted from person-to-person.
	CRITERIA	JUDGMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	How substantial are the undesirable anticipated effects?	*Trivial* ☐ *Small* ☒ *Moderate* ☐ *Large* ☐ *Don't know* ☐ *Varies* ☐	A GRADE assessment was completed. The following data include all reported serious adverse events (SAEs), whether assessed as related or unrelated. Evidence used to evaluate SAE was from 16 studies, including eight RCTs, four observational studies, and four post-marketing assessments. • SAEs within 1 month after either JE-VC dose were reported in 29 (1%) of 4,855 subjects in 12 clinical trials. • SAEs within 6 to 7 months after the first JE-VC dose were reported in 72 (1%) of 5,269 subjects in five clinical trials. • When data from RCTs were combined and weighted using a random effects model, there was no significant difference in proportions of subjects with SAEs within 1 month of JE-VC or the comparison vaccines (eight RCTs), or within 6 to 7 months of JE-VC and the comparison vaccines (two RCTs). • Three large post-marketing surveillance evaluations reported 1.1–1.8 serious adverse events per 100,000 doses distributed, and a retrospective chart review for medical visits following administration of JE-VC	In considering rates of adverse events, it is important to understand that causality usually cannot be determined, especially in surveillance data when reported events occur among persons who have often received multiple vaccines. The relatively small numbers of subjects in the clinical trials limited the ability to detect rare SAEs, but the findings from post-marketing

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			to 145 children detected no SAEs. These rates are similar to or lower than rates from post-marketing adverse event surveillance for other vaccines, including quadrivalent human papillomavirus vaccine, 23-valent pneumococcal polysaccharide vaccine, yellow fever vaccine, and live attenuated herpes zoster vaccine. • No patterns in the timing or types of serious adverse events were identified. Evidence used to evaluate adverse events of special interest was from 12 studies, including eight clinical trials and four post-marketing assessments. • Fever within 7 days after either JE-VC dose was reported in 296 (8%) of 3,892 subjects in seven studies. Proportions of subjects with fever in individual studies ranged from 0% to 21% with differences likely related to the different age groups studied, variable study locations, differences in study methodology, and possibly less precision in some smaller studies. • Rash within 7 days after either JE-VC dose was reported in 81 (2%) of 3,892 subjects. • Hypersensitivity or urticaria within 1 month was reported in 10 (<1%) of 3,868 JE-VC recipients in six studies. • Neurologic adverse events (excluding headache) within 1 month were reported in 26 (1%) of the 3,668 recipients. • Medically attended adverse events within 1 month were reported in 571 (14%) of 3,947 subjects. Proportions in individual studies ranged from 0 through 19%; the two studies with the highest percentage of subjects with medically attended adverse events were conducted among children in the Philippines and elderly adults in Europe.	surveillance following distribution of >1 million doses provide indirect but reassuring supportive data on the vaccine's safety.

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			• When data from RCTs were combined and weighted using a random effects model, there were no significant differences in the proportions with any of these adverse events of special interest between recipients of JE-VC and comparison vaccines. • In passive post-marketing surveillance the reported incidence of hypersensitivity was 3.0–4.4 per 100,000 doses distributed and of neurologic adverse events (excluding headache) was 0.2–1.1 per 100,000 doses distributed. In a post-marketing adverse event surveillance study conducted among military personnel and involving retrospective review of medical records, rates for hypersensitivity and neurologic reactions were 24.8 and 22.0 per 100,000 doses administered, respectively. The higher reported rates in this surveillance reflected the different active surveillance approach. **Overall conclusion:** The work group concluded the undesirable anticipated effects were small.	
	Do the desirable effects outweigh the undesirable effects?	*Favors intervention* ☒ *Favors comparison* ☐ *Favors both* ☐ *Favors neither* ☐ *Unclear* ☐	JE-VC is the only JE vaccine licensed and available in the United States. With no alternative vaccine, this assessment focused on comparing the balance of risks and benefits of JE-VC. Evidence that the desirable effects outweigh the undesirable effects includes: • High seroprotection rates at both 1 month and 5 to 6 months after the 2-dose primary series of JE-VC. • Serious adverse events and adverse events of special interest are rare in clinical trials and safety profile is similar to other vaccines with good safety profiles, or to adjuvant (aluminum hydroxide) alone. • Reassuring data from post-marketing surveillance following distribution of >1 million doses in the United States, with reported rates of serious adverse	

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			events similar to rates reported for other routinely used vaccines. • No patterns in the timing or types of serious adverse events identified in the clinical trials or surveillance data. **Overall conclusion**: In general, with high seroprotection rates following vaccination and with no important safety concerns identified, the work group considered the desirable effects of a vaccine to prevent a rare but potentially serious, untreatable disease outweighed the undesirable effects of vaccination. However, as with any vaccine, rare serious adverse events can occur and so for some travelers with lower risk itineraries, even a low probability of vaccine-related serious adverse events might be higher than the risk for disease. Therefore, for each traveler, a healthcare provider should consider and discuss the balance of desirable and undesirable effects and the traveler's risk based on itinerary and activities, and JE vaccine should be targeted to travelers who are at increased risk for disease.	
	What is the overall certainty of this evidence for the critical outcomes?	Effectiveness of the intervention No included studies ☐ | 4 Very low ☐ | 3 Low ☐ | 2 Moderate ☐ | 1 High ☒ Safety of the intervention No included studies ☐ | 4 Very low ☐ | 3 Low ☐ | 2 Moderate ☒ | 1 High ☐	The GRADE approach was followed for assessing type of evidence. • Overall evidence type 1 for vaccine effectiveness using seroprotection as the endpoint. • Overall evidence type 2 for safety, with evidence type downgraded because of risk of bias due to inadequate blinding of study participants and personnel. **Overall conclusion**: Evidence is type 1 (i.e., high) for vaccine effectiveness using seroprotection as the endpoint and type 2 (i.e., moderate) for safety.	For serious adverse events at 1 month, there was some concern about inconsistency and imprecision in the RCTs. However, complementary information from surveillance assessments and observational studies provided additional data supportive of the vaccine's safety.

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VALUES	Does the target population feel that the desirable effects are large relative to undesirable effects?	*No* ☐ *Probably no* ☐ *Uncertain* ☐ *Probably yes* ☐ *Yes* ☐ *Varies* ☒	A population survey was conducted using the Porter Novelli Public Services Styles (*SpringStyles*) survey mechanism • Panel of participants representative of the non-institutionalized U.S. population and randomly recruited by mail. • Survey response rate was 6,427 (59%) of 10,904 adults; among respondents, 6,384 (99%) completed the JE question. Participants were asked two questions: • You are going on a trip to another country. You have a one in a million chance of getting a disease. About one-third of people who get the disease will die and one-third of people will have a permanent disability like problems with walking or thinking clearly. There is a vaccine that prevents the disease. It is safe although on rare occasions can cause serious side effects. It costs $600 and is not covered by insurance. How likely are you to get the vaccine? (Very likely/Somewhat likely/Not sure/Somewhat unlikely/Very unlikely) • Which factors were most important in deciding whether you would get the vaccine? (One or more factors can be selected of Chance of getting the disease/Chance of dying or being disabled/The vaccine is safe/Chance of serious side effects/Cost of the vaccine/I do not get any vaccinations/Other reasons not listed) Demographics of respondents • Male: 45% • Median age 51 years (range: 18-94 years) • White, non-Hispanic: 74% • At least some college or higher education: 72% • Household income ≥60K: 61% Results	

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			• Likelihood of getting JE vaccine was "very likely" (16%), "somewhat likely" (16%), "not sure" (25%), "somewhat unlikely" (17%) and very unlikely (26%). **Overall conclusion:** The results suggest there is variability in the population perception of whether the potential benefits of vaccination outweigh harms.	
	CRITERIA	JUDGMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	Is there important uncertainty about or variability in how much people value the main outcomes?	*Important uncertainty or variability* ☒ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☐ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐	Among the groups "likely" to choose vaccination influential factors were chance of getting disease, and dying or being disabled • Comparing "very likely' and "somewhat likely" groups, latter group had additional concern about cost and chance of serious side effects Among the groups "unlikely" to choose vaccination • Cost most important factor • Chance of getting the disease also major factor **Overall conclusion:** The survey results suggest that the population has different perceptions of disease risk and value of vaccination. While some of the population clearly value the availability of a vaccine to prevent a rare disease with potentially serious outcomes and no treatment, others were less likely to place value on it when the vaccine is expensive and, while safe, has the possibility of rare serious side effects. Disease risk was considered a reason to both receive and not receive the vaccine. There is clearly substantial variability in perception and tolerance of risk with an important impact on decision-making on vaccination choices.	

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ACCEPTABILITY	Is the intervention acceptable to key stakeholders?	*No* ☐ *Probably no* ☐ *Uncertain* ☐ *Probably yes* ☒ *Yes* ☐ *Varies* ☐	Travel medicine practitioners were considered an important stakeholder. The work group could not identify a feasible mechanism to survey U.S. travel medicine practitioners within the timeframe available. Four members of work group who are travel medicine practitioners and members of the International Society of Travel Medicine played an active role in discussions about the recommendations. Several publications authored by U.S. health care providers have included opinions on the existing ACIP JE vaccine recommendations, ranging from suggesting limited use based on an individual assessment for each traveler to broader consideration for any traveler to a rural or peri-urban area irrespective of duration of travel or itinerary. Valneva sponsored an "Expert Advisory Group on JE Prevention" that has had several meetings and written three letters to ACIP in January 2015, April 2017, and October 2017. The group has urged broadening of the recommendations to include traveler groups the work group considers ill-defined for being at higher risk. The work group reviewed the letters and had two travel medicine practitioners with dissenting opinions on the recommendations present to the work group. It is unknown how representative this group might be of other travel medicine practitioners. The manufacturer has similarly suggested broadening of the recommendations, but due to a conflict of interest, acceptability to the manufacturer was given low priority. For the public, the proposed recommendations are likely to be acceptable as they describe and target vaccination of travelers with the highest risk for infection and so limit the number of travelers for whom an expensive vaccine for a very low risk disease might be	

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			recommended. Most travelers are likely to value a discussion of the risks and benefits of vaccination, including consideration of the traveler's tolerance of risk, while others might prefer more concrete recommendations that clearly define who should receive vaccine based on a specific factor. Some travelers who have an insurer that covers travel vaccines might prefer a recommendation for vaccination for all travelers. **Overall conclusion**: While there is some variability in stakeholders thoughts on the recommendations, there is stakeholder agreement that • Overall, JE risk is low for most travelers • There is need to inform travelers about risks and prevention measures for JE • Vaccine should be targeted to travelers at higher risk All members of the work group agreed the vaccine recommendations were acceptable, and felt they will probably be acceptable to most stakeholders as they are based on individual clinical decision-making with consideration of risks and benefits of vaccination.	
RESOURCE USE	Is the intervention a reasonable and efficient allocation of resources?	*No* ☐ *Probably no* ☐ *Uncertain* ☐ *Probably yes* ☒ *Yes* ☐	JE vaccination is cost-effective or cost-saving for local populations in JE endemic countries. However, JE vaccination is not expected to be cost effective among travelers as there is 1) a substantially lower risk of disease, and 2) use of much lower cost vaccines in most vaccination programs in Asia. There were several general resource considerations noted by the work group when discussing JE vaccination for travelers. From a societal perspective, JE vaccination is probably not an efficient use of resources. The vaccine is expensive and the disease is rare. However, the question of resource use is less relevant for travel vaccines which are usually paid for by the travelers themselves and are not covered under the Vaccines for Children program or by most insurance plans. Travelers	The vaccine is expensive which raises equity issues. The cost could lead to health disparities as some travelers might not be able to afford the vaccine. However, the vaccine recommendations cannot address this issue.

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			make individual decisions on vaccination. Mortality and disability rates following disease are high, and about one third of participants in the survey described above indicated vaccination was probably a reasonable investment. Nonetheless, there are opportunity costs for travelers in purchasing this vaccine compared with an alternative preventive measure. The work group did not consider a cost-effectiveness analysis of JE-VC essential. However, the work group decided to perform a comparative analysis of different vaccination strategies to understand the numbers needed to vaccinate and cost per case averted for travelers with different itineraries and disease risk, and the cost implications of expanding the existing JE vaccine recommendations to a broader group of travelers. A comparative analysis of strategies for JE vaccination for U.S. travelers to Asia was performed by CDC's Health Economics and Modeling Unit. An analytic horizon of 6 years was used, but productivity losses were evaluated over average life expectancy. The analysis compared JE vaccination in three groups. • Risk group l included travelers who plan to spend ≥1 month in JE endemic areas and approximates the group for whom JE vaccine is recommended under the ACIP guidelines. • Risk group 2 included travelers who will spend <1 month in JE endemic areas, with at least 20% of their time doing outdoor activities in rural areas. This group approximates travelers for whom JE vaccination should be considered after evaluating their itinerary and weighing the benefits, risks, and costs. • Risk group 3 included the remainder of shorter-term and lower-risk U.S. travelers to Asia for whom JE vaccination is not recommended.	

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			To prevent one JE case, the number of travelers who would need to be vaccinated was 0.7 million in Risk group 1, 1.6 million in Risk group 2, and 9.8 million in Risk group 3. The cost to prevent one JE case from a societal perspective was approximately $0.6 billion for Risk group 1, $1.3 billion for Risk group 2, and $7.9 billion for Risk group 3. The variable with the greatest influence on the cost-effectiveness of vaccination was disease incidence among travelers. As baseline incidence is based on reported JE cases, to address any uncertainty about the sensitivity of surveillance, a sensitivity analysis was conducted increasing baseline incidence 100 times. In this analysis, the numbers needed to vaccinate to prevent a case were 7,000, 16,000 and 98,000, and the cost per case averted was $5 million, $12 million, and $78 million in each Risk group, respectively. The cost to society to prevent one additional case of JE if JE vaccination recommendations were expanded would be • $1.6 billion if expanding from Risk group1 to Risk groups 1 and 2. • $14.6 billion if expanding from Risk groups 1 and 2 to all travelers. **Overall conclusion**: The work group decided the question of whether the intervention was a reasonable and efficient allocation of resources was not directly applicable to JE vaccination as travel vaccines are usually paid for by the travelers themselves who make individual decisions on vaccine purchase. In general, JE vaccination cannot be considered an efficient use of societal resources as it is an expensive vaccine for a low risk disease. Nonetheless, the comparative analysis supports the proposed tiered JE vaccine	

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			recommendations as it indicated a large increased cost to society to prevent a case of JE when including Risk groups 1 and 2 compared with Risk group 1 alone, supporting a more cautious approach or "consideration" of vaccination for those in Risk group 2. In addition, there was a very large increased cost to society if Risk group 3 was included, which does not support a broad recommendation of JE vaccination for all travelers. Overall, vaccine recommendations targeted to higher risk groups are probably a reasonable allocation of resources as the financial implications of vaccine purchase will be borne by travelers most at risk of a severe disease who will therefore receive the most benefit.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably no* ☐ *Uncertain* ☐ *Probably yes* ☒ *Yes* ☐ *Varies* ☐	JE vaccination is provided by generalist and specialist health care providers. Administration is feasible as part of a pre-travel consultation. Barriers to implementation of risk-based vaccine recommendations might include lack of understanding of factors that might increase the risk for JE, and therefore which travelers might benefit most from vaccination. However, specific information is provided in a table accompanying the recommendations and other resources also are readily available. **Overall conclusion**: Risk-based recommendations are probably feasible to implement.	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced* or *uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings	There is insufficient evidence to determine the balance of consequences
	☐	☐	☐	☒	☐	☐

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Overall, the work group determined the desirable consequences probably outweigh undesirable consequences in most settings when risk-based recommendations are appropriately implemented.			
Is there sufficient information to move forward with a recommendation? Yes x No ☐			
Type of recommendation	We do not recommend the intervention ☐	We recommend the intervention for individuals based on clinical decision-making ☒	We recommend the intervention ☐

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Recommendation	**Recommendations for the Prevention of JE Among Travelers** JE is a very low risk disease for most U.S. travelers to JE-endemic countries. However, some travelers will be at increased risk of infection based on their planned itinerary. Factors that increase the risk of JE virus exposure include: 1) longer duration of travel, 2) travel during the JE virus transmission season, 3) spending time in rural areas, 4) participating in extensive outdoor activities, and 5) staying in accommodations without air conditioning, screens, or bed nets (Box). Healthcare providers should assess each traveler's risk for mosquito exposure and JE virus infection based on their planned itinerary, and discuss ways to reduce their risk. All travelers to JE-endemic countries should be advised to take precautions to avoid mosquito bites to reduce the risk for JE and other vector-borne diseases. These precautions include using insect repellent, permethrin-impregnated clothing, and bed nets, and staying in accommodations with screened or air-conditioned rooms. For some people who might be at increased risk for JE based on travel duration, season, location, activities, and accommodations, JE vaccine can further reduce the risk for infection. The decision whether to vaccinate should be individualized and consider the: 1) risks related to the specific travel itinerary, 2) likelihood of future travel to JE-endemic countries, 3) high morbidity and mortality of JE when it occurs, 4) availability of an effective vaccine, 5) possibility, but low probability, of serious adverse events following vaccination, and 6) traveler's personal perception and tolerance of risk. JE vaccine is recommended for persons moving to a JE-endemic country to take up residence, longer-term (e.g., ≥1 month) travelers to JE-endemic areas, and frequent travelers to JE-endemic areas. JE vaccine also should be considered for shorter-term (e.g., <1 month) travelers with an increased risk of JE based on planned travel duration, season, location, activities, and accommodations (Box). Vaccination also should be considered for travelers to endemic areas who are uncertain of specific duration of travel, destinations, or activities. JE vaccine is not recommended for travelers with very low risk itineraries, such as shorter-term travel limited to urban areas or travel that occurs outside of a well-defined JE virus transmission season.

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Box 1. Factors that increase risk for Japanese encephalitis among travelers

Duration

- Highest incidence of disease has been reported among longer-term travelers.
- Although no specific duration of travel puts a traveler at risk for JE, longer-term travel increases the likelihood that a traveler might be exposed to an infected mosquito.
- Longer-term travel includes cumulative periods in endemic areas; this includes frequent travelers, and persons residing in urban areas who are likely to visit higher risk rural areas.

Season

- JE virus transmission occurs seasonally in some areas, and year-round in other areas.
- Information on expected JE virus transmission by country is available on the CDC website (see Japanese encephalitis chapter in CDC Health Information for International Travel [the Yellow Book]). These data should be interpreted cautiously because JE virus transmission varies within countries and from year to year.

Location

- Highest risk occurs from mosquito exposure in rural or agricultural areas.
- Mosquitoes that transmit JE virus typically breed in flooded rice fields, marshes, and other stagnant collections of water.
- Some cases have been reported among travelers to coastal areas or resorts located in or adjacent to rural or rice growing areas.
- JE can occur in large, focal outbreaks indicating extensive active JE virus transmission in those areas.

Activities

- The mosquitoes that transmit JE virus feed most often in the outdoors, particularly from sunset through dawn, so examples of activities that increase risk include:
    - Outdoor recreation such as camping, hiking, trekking, biking, rafting, fishing, hunting, or farming.
    - Spending substantial time outdoors, especially during the evening or night.

Accommodations

- Accommodations without air conditioning, screens, or bed nets increase risk of mosquito exposure.

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Additional considerations (optional)	Among the shorter-term travelers for whom vaccination would be "considered" rather than "recommended" there was no consistent risk factor, destination, or feature to enable further targeting of recommendations. This suggests the only way to prevent every case would be to recommend vaccination for all travelers; however, based on risks and benefits, the work group members felt vaccine recommendations should be targeted to a subset of travelers with greater risk of infection.

This Evidence to Recommendation table is based on the GRADE Evidence to Decision framework developed through the *DECIDE* project. Further information is available at http://www.decide-collaboration.eu/evidence-decision-etd-framework